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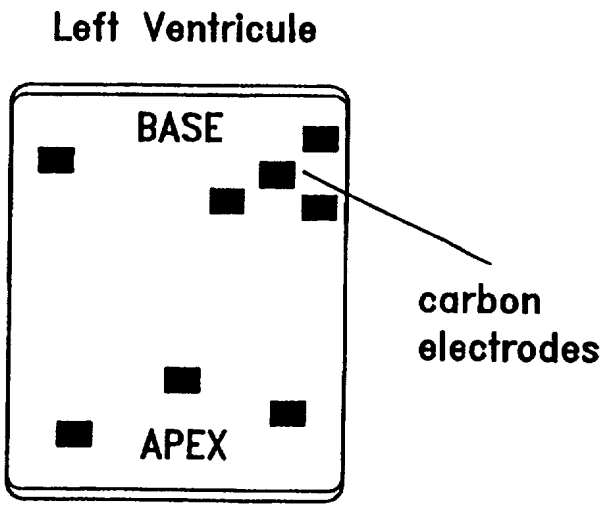
(54) **Title:** APPARATUS AND METHOD FOR CONTROLLING THE CONTRACTILITY OF MUSCLES

(57) **Abstract**

An apparatus comprises circuitry for creating a non-excitor electric potential between at least two points located in the vicinity of a muscle. A method is provided which employs the apparatus for reducing the contraction force of a muscle.



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APPARATUS AND METHOD FOR CONTROLLING THE CONTRACTILITY OF MUSCLES

Field of the Invention

The present invention relates to the field of medicine. More particularly, the invention relates to means for controlling the contractility of muscles.

Background of the Invention

Many activities of the human body involve the contraction of muscles. For instance, movement of the limbs, breathing activity, etc. The most complex and vital muscular activity of the human body is that of the heart, which functions as a pump and which, by contracting at the required times and in the required manner, controls the flow of blood throughout the body.

The heart is composed of different parts, which contract differently and with different timing, in order to permit the aforementioned pumping activity. The contraction of the heart is controlled by electric stimuli, which are generated at the cellular level by chemical reaction. However, it is well known in the art to control such activity, i.e., the timing of the contraction of the cardiac muscle, by the action of externally applied electric stimuli, through the so-called "pace maker".

In a copending PCT patent application of the same applicants herein, No. PCT/IL97/00012, filed January 8, 1997, the specification of which is incorporated herein by reference, there is described a method and apparatus for increasing the contraction force of at least a portion of a heart chamber, which method comprises applying a non-excitatory electric field, for a predetermined period of time, at a delay after activation, which causes the contraction force to be increased. Substantial increases in the force of contraction are obtained, typically - but non-limitatively - in the order of 5% - 50%. The increase in cardiac output is useful in order to obviate cardiac insufficiency due to a variety of pathological situations, e.g., the reduction of cardiac output due to the implantation of a pace maker, the insufficiency due to the results of the malfunctioning of a portion of the cardiac muscle, etc.

While means are now available in order to control, improve and increase the activity of the heart, not enough attention has been paid in the art to the reduction of heart muscle contractility, and no means have been provided for controlling the heart in a localized and reversible manner. The ability to control the reduction of heart muscle contractility, however, is of paramount importance in a great many situations, some of which are listed below:

Heart Surgery: Heart surgery, as performed according to the known art, requires that ventricular fibrillation be induced on the patient's heart, and that the patient be connected to a heart and lung machine, in order to perform various operations, e.g., a bypass operation. The need to induce of ventricular fibrillation not only complicates the surgery and renders it expensive, but also increases the danger of post-operation trauma, such as the formation of thrombi and emboli. It is therefore clear that it would be highly desirable to be able to perform heart surgery, such as bypass operations, without the need to induce ventricular fibrillations, and without side effects of cardioplagia, by controllably and reversibly reducing the activity of the cardiac muscle, in the area where the operation is performed, to a level which makes it possible for the surgeon to operate with the required degree of accuracy. This is also important in performing minimal invasive surgery using thoracoscope, to enable the surgeon to better control the operation.

Healing of the Cardiac Muscle: Reduction of the cardiac muscle contractility is of importance during the healing of the cardiac muscle after myocardial infarct. According to the known art there are no means which permit a selective reduction of the contractility of an affected area, so as to reduce the oxygen consumption of a hibernated area, so as to help them to overcome the critical period and heal. The hibernating myocardium is temporary "asleep" and can wake up to restore the function

when the blood supply is restored. However, a healing period can be necessary, in which oxygen demand must be kept low.

Treating Congenital and Acquired Hypertrophic Cadiomyopathy (HCM): The ability to reduce muscle contractility can be of importance in the treatment of this disease, which is characterized by a dynamic pressure gradient in the subaortic area that divides the left ventricle into a high-pressure apical region and a lower-pressure subaortic region. The ability to reduce muscle contractility is therefore useful to obviate this disproportion and to reduce the pressure gradient.

Cardiac Ablation: Cardiac ablation is a procedure by which the cardiac muscle is treated by burning off selected and localized areas with a laser light or other energy source. A detailed discussion of cardiac ablation techniques can be found, e.g., in the reference book by Mark E. Josephson: *"CLINICAL CARDIAC ELECTROPHYSIOLOGY, Techiniques and Interpretations"*, 2nd Edition, R. Kenneth Russy Ed., Ch. 16: *"Surgical and Nonsurgical Ablation in the Therapy of Arrhythmias"* Lea & Febiger, Malvern, PA. The ablation is performed on a beating heart, and the art has so far failed to provide means by which the contractility, i.e., the movement, of the treated area can be reduced.

Selective Contractility Reduction: While it is known in the art to reduce the contractility of the heart as a whole, by means of systemic

drugs, the art so far has not been able to provide means by which a desired portion of the heart can be caused to reduce its contractility, which other portions function with an unchanged contractility, or even with a contractility which has been increased as described and claimed in the aforementioned PCT patent application. This option, unavailable according to the known art, is important in order to compensate for the temporary reduction in contractility of one area, by the increased contractility of another.

Interim Treatment: In many cases, e.g., intractable angina, there is a need to reduce oxygen consumption of the cardiac muscle while treatment is being considered. The known art does not provide any means to reduce the contractility of the heart muscle in a localized manner, thus reducing the oxygen consumption until other treatment is initiated.

It is therefore highly desirable to provide means which permit the reduction of the contractility of the cardiac muscle, in an controlled manner. It is an object of the present invention to provide apparatus and a method by which the contractility of a portion of the cardiac muscle can be reduced in a controlled manner.

It is another object of the invention to provide apparatus and a method for facilitating cardiac surgery on a beating heart.

It is still another object of the invention to provide apparatus and a method for promoting the healing of the hibernated area of the cardiac muscle after myocardial infarct.

It is yet another object of the invention to provide apparatus and a method for selectively reducing the oxygen consumption of a portion of a heart.

Other objects and advantages of the invention will become apparent as the description proceeds.

SUMMARY OF THE INVENTION

The invention relates to apparatus comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of a muscle.

In the context of the present invention, the terms "non-excitatory current", or "non-excitatory potential", or "non-excitatory signal", mean a signal which does not cause a propagating action potential in the muscle cells (which may start a new pacing or contraction of the muscle). In other words, the non-excitatory electric stimulation effected by a non-excitatory electric pulse is such that it does not induce propagating activation potentials in the cardiac muscle cells. Rather, such pulses affect the response of the heart muscle to the action potentials, by modulating cell

contractility within selected segments of the cardiac muscle. As described in the abovementioned PCT patent application PCT/IL97/00012, the inventors have found that by applying non-excitatory electrical stimulation pulses of suitable strength, appropriately timed with respect to the heart's electrical activation, the contraction of the selected segments can be increased or decreased, thus increasing or decreasing the stroke volume of the heart.

There may be various reasons for a signal to be non-excitatory. Two main types of non-excitatory signals to be used in conjunction with the invention are: 1) A signal which, independently of its magnitude, is applied during the refractory period, and therefore does not cause a new contraction, even though its magnitude may be above threshold values for pacing; 2) A signal which is sub-threshold for pacing and, therefore, no matter when applied, does not cause a new contraction to take place.

According to one embodiment of the invention, the apparatus comprises circuitry for controlling the start time of the electric potential generated between said at least two points. According to another preferred embodiment of the invention the apparatus comprises circuitry for controlling the duration of the electric potential generated between said at least two points. According to yet another preferred embodiment of the invention the apparatus comprises circuitry for controlling the magnitude of the electric potential generated between said at least two points.

In another aspect, the invention is directed to apparatus comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of a muscle.

According to one embodiment of the invention, the apparatus comprises circuitry for controlling the start time of the electric current flowing between said at least two points. According to another preferred embodiment of the invention the apparatus comprises circuitry for controlling the duration of the electric current flowing between said at least two points. According to yet another preferred embodiment of the invention the apparatus comprises circuitry for controlling the magnitude of the electric current flowing between said at least two points.

The apparatus according to the invention, as described above, is suitable for use in reducing the contraction force of a muscle, such as a cardiac muscle.

The circuitry for creating a non-excitatory electric potential between said at least two points may be of many different types and preferably comprises one or more electrode. Illustrative and non-limitative examples of suitable electrodes include carbon electrodes.

The apparatus of the invention may be provided in various forms and may be, e.g., an insertable device, an extra corporal device or an implantable device.

According to a preferred embodiment of the invention the circuitry for controlling the start time and/or duration of the electric potential is synchronized to heart activity. Furthermore, such circuitry may operate not at every beat of the heart, e.g., every 1, 2 or 3 beats of the heart.

According to a preferred embodiment of the invention the non-excitatory electric current is a DC electric current. According to a preferred embodiment of the invention, the apparatus further comprises signal generation circuitry for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

The apparatus according to the invention is particularly useful for performing heart surgery, such as a bypass operation.

The apparatus of the invention is also useful in many other applications, such as for promoting the healing of the hibernated area of the cardiac muscle after myocardial infarct, for promoting the healing of an ischemic area of the cardiac muscle, for treating congenital or acquired

hypertrophic cardiomyopathy, and for aiding in performing cardiac ablation.

In another aspect the invention is directed to apparatus for reducing the contraction force of a muscle, comprising:

- means for creating an electric potential between at least two points located in the vicinity of the muscle;

- means for causing a non-excitatory DC electric current to flow between said at least two point, if desired; and

- means for controlling the start time, duration and magnitude of the non-excitatory electric potential and/or of the non-excitatory electric current flowing between said at least two points.

According to a preferred embodiment of the invention the apparatus comprises:

- means for creating an electric potential between at least a pair of electrodes in the vicinity of the muscle at at least two root locations;

- means for causing a non-excitatory DC electric current to flow between said at least two root locations when desired; and

- means for controlling the start time, duration and magnitude of the non-excitatory electric potential and/or of the non-excitatory electric current flowing between said at least two root locations.

By "root location" it is meant to indicate the vicinity of the muscle where the electrodes are located, which may be distinct from the area which is affected by the current flowing between them. As will be appreciated by the skilled person, due to the very complex nature of the electric behavior of the cardiac muscle, it is possible that positioning an electrode at a given location will affect another, more remote portion of the muscle. Therefore, the root location is not necessarily the center or any other portion of the treated area, but it is only a location, near the muscle, where an electrode will be positioned.

In yet another aspect, the invention is directed to a method for reducing the contraction force of a muscle, comprising creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points.

In still a further aspect, the invention is directed to method for reducing the contraction force of a muscle, comprising causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points.

The non-excitatory electric signal can be a DC signal, and further a complex signal can be generated by superimposing on the DC signal one or more waveforms of given frequency and amplitude. According to a preferred embodiment of the invention the non-excitatory DC electric signal is synchronized to heart activity, and can be imparted not at every beat of the heart, e.g., every 1, 2 or 3 beats of the heart.

Also encompassed by the invention is a method for performing heart surgery, comprising reducing the contraction force of a treated area of the cardiac muscle, according to the invention, and thereafter performing surgery thereon.

The invention can be usefully exploited in a variety of situations involving heart surgery, such as in a bypass operation.

Additionally, according to the invention there is provided a method for promoting the healing of the cardiac muscle after myocardial infarct, comprising creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points, said electric potential being of an intensity and polarity

suitable to obtain the desired reduction in muscle contraction at the affected heart area.

In another preferred embodiment of the invention there is provided a method for promoting the healing of the cardiac muscle after myocardial infarct, comprising causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, said electric current being of an intensity and polarity suitable to obtain the desired reduction in muscle contraction at the affected heart area.

The invention further provides a method for treating congenital or acquired hypertrophic cardiomyopathy, comprising reducing the contraction force of a the heart muscle, according to the invention, for a suitable period of time.

The invention is also useful in performing other procedures, such as for performing cardiac ablation, by reducing the contraction force of the area of the cardiac muscle to be ablated, and thereafter performing the ablation thereon.

It should also be noted that, when the reduction in contractility is effected on a localized area, it is possible, and it may be useful in some cases, to increase the cardiac muscle contractility at locations other than the treated location. This can be effected as described in greater detail in the aforementioned PCT application PCT/IL97/00012.

In another aspect, the invention is directed to a method for the interim treatment of a heart in need of reducing oxygen consumption, comprising reducing the contraction force of a the heart muscle, according to the invention, thereby reducing the oxygen consumption of the heart.

According to a preferred embodiment of the invention, there is provided a method for reducing the contraction force of a muscle, comprising:

- providing means for creating an electric potential between at least two points located in the vicinity of the muscle;

- providing means for causing a non-excitatory DC electric current to flow between said at least two point;

- providing means for switching the current polarity between said at least two points; and

- providing means for controlling the start time, duration and magnitude of the electric current flowing between said at least two points.

According to one preferred embodiment of the invention, there is further provided a method, comprising:

- providing an electric potential between at least a pair of electrodes in the vicinity of the muscle at at least two root locations;

- causing a non-excitatory DC electric current to flow between said at least two contacting locations;

- providing means for switching the current polarity between said root locations; and

- controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations, so as to obtain the desired reduction in muscle contraction.

The apparatus employed to carry out the method of the invention can be of different construction, as will be apparent to the skilled person. One example of apparatus suitable for carrying out the invention is described in detail and claimed in a copending PCT patent application of the same applicants herein, entitled "Cardiac Output Controller", filed on the same day as the present application and identified as Attorney's Docket 27068, the description of which is incorporated herein by reference. Another example of suitable apparatus, coupled to a pacemaker device, is the subject of another copending PCT patent application of the same applicants herein, entitled "Cardiac Output Enhanced Pacemaker", filed on the same day as the present application and identified as Attorney's Docket 27181, the specification of which is also incorporated herein by

reference. However, as said, the invention is not intended to be limited to any particular construction of device used to carry it out.

As said, while a DC current is typically used as the base line for the non-excitatory signal, it is possible, and in some applications it may be desirable, to supply a signal which is a complex signal, for instance, a signal generated by superimposing an AC current on the DC base signal, so as to generate a waveform of varying envelope. Any suitable signal can be superimposed, having any shape, e.g., square wave or sinusoidal wave, as will be apparent to the skilled person. Thus, according to one preferred embodiment of the invention the apparatus further comprises means for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

It should also be appreciated that the apparatus of the invention operates with synchronization of the cardiac activity, since lack of synchronization may result in ventricular fibrilation. Synchronization of the NT-signal can be effected on the pacing signal, if a pace maker or other pacing apparatus is used, or to the cardiac activity of the patient. In the examples to follow a pacing signal is used, for the sake of precision in operation of the muscle the activity of which is being sampled.

As will be appreciated by the skilled person, the actual set of operating parameters used (current, length of pulse, number of electrodes, lag after

pacing signal, etc.), will be dependent on the specific use made of the invention, and the skilled person will be able to devise the optimal set of parameters for a given application. Some non-limitative operating ranges in which cardiac muscle reacts according to the invention are given here for the sake of illustration only, it being understood that operation outside such ranges is of course possible under various conditions: Current: 0.01 - 10 mA; Length of Pulse: 1-998 milliseconds with a pacing of 1 Hz, and 1-498 milliseconds with a pacing of 2 Hz; Delay after Pacing Signal: 1 milliseconds and above. Where no pace maker is used, the delay is preferably calculated from the natural pacing of the patient's heart, or from the local activation time of the muscle.

As stated, while the invention can be exploited with other muscles, the most important muscle to be treated according to the invention is the cardiac muscle. While a variety of electrodes can be used, and the invention is in no way limited to any particular type of electrode, particularly preferred suitable electrodes for this purpose are, e.g., carbon electrodes.

As will become apparent to the skilled person by the description to follow, the determination of the optimal parameters for a given subject can be easily be effected at the beginning of any given procedure and progressively adjusting the various parameters (current intensity, pulse duration, time lag from pacing), so as to reach the desired decrease in

cardiac contractility. Of course, other parameters may be optimized by the physician on a given patient, in order to obtain the best performance when reducing the contractility of the muscle. Such parameters include, e.g., the distance between the root location of the electrodes, and the surface area of the electrodes. The distance will influence the size of the area that is affected by the electric current, and when the root locations are placed far apart, a stronger current may be required. Of course, larger electrodes (with greater surface area) may be needed to deliver more current. As will be apparent to the skilled person, the area affected by the signal may be very small (e.g., 2 cm^2), or substantially the whole heart can be affected, as illustrated in Fig. 7, described in detail below.

Brief Description of the Drawings

The above and other characteristics and advantages of the invention will be more readily apparent through the following detailed description of preferred embodiments thereof, with reference to the appended drawings, wherein:

- Fig. 1 is a schematic representation of the experimental setup used in the Acute Cardiac Inhibition experiments in anaesthetized dogs (such as used in the experiments detailed in Fig. 5);

- Fig. 2 shows the results obtained in Example 1:

  Fig. 2A shows the timing and magnitude of the electric signal (NT-signal); and

Fig. 2B shows the force of contraction of the muscle;

- Fig. 3 (A, B) shows the results obtained in the same experimental setup of Example 1, but on a different time scale;

- Fig. 4 shows the results obtained in Example 2:

Fig. 4A shows the behavior of the force in the different situations;

Fig. 4B shows a summary of data from three experiments where decrease in muscle contractility was achieved by changing the polarity of the signal;

- Fig. 5 shows the results obtained in Example 3:

Fig. 5A shows the decrease in LVP pressure;

Fig. 5B shows the decrease in output (mean aortic flow);

- Fig. 6 shows the results obtained in Example 4:

Fig. 6A is the decrease in LVP pressure;

Fig. 6B is the decrease in output (blood flow rate);

- Fig. 7 shows the results obtained in Example 5:

Fig. 7A shows the decrease in pressure;

Fig. 7B shows the decrease in blood flow rate;

- Fig. 8 shows the results obtained in Example 6;

- Fig. 9 shows the results obtained in Example 7;

- Fig. 10 shows the effect of applying a long NT-signal; and

- Fig. 11 is a schematic representation of an apparatus according to one embodiment of the invention.

Definitions

The following terms and abbreviations, used throughout this specification, are defined below, for the sake of clarity:

b.p.m. = Beats per minute

HMC = Hypertrophic Cardiomyopathy

I.M. = Intramuscular

IV = Intra Venous

LV = Left Ventricle

LVP = left ventricular pressure

NT Signal = Non-Excitatory Signal

RV = Right Ventricle

VF = Ventricular Fibrillation

Detailed Description of Preferred Embodiments

The invention will now be illustrated through *in vitro* and *in vivo* experiments. Experiments *in* vitro were carried out using isolated rabbit papillary muscle, and the protocol for its isolation is detailed below. Experiments *in vivo* were carried out on dogs, and the protocol for such experiments is also detailed below.

Isolated Papillary Muscle Protocol

Animals: New Zealand white rabbits (males) from Israel (Yokneam) or an hybrid of New Zealand White and local albino rabbits (males, AniLab, Rehovot) are kept in room temperature, 2-3 per cage (35x55x65 cm), under natural light conditions. Daily feeding of dry food (Rabbit Mix- Code 590), and unlimited water supply. The cages and the room are cleaned daily,

Instruments:

A. for solution making: Scales (by Mettler toledo, model P8303, Max 310gram, d=1mGram) **magnetic stirrer.** by Freed electric. Weights 10Kg (d=50gram) by Moznei Shekel, Gas tanks with mixed 95% O_2 +5% CO_2" pressure regulators, pH meter by Mettler Toledo, model 320 PH, ice machine 45 Labotal.

B. for the in-vitro papillary muscle preparation

Dissection chamber (HSH, Hugo Sachs Elektronik, Germany), Steered organ bath type 813 (I-18E) including temperature controller type 319, Force Transducer type F30 with amplifier type 660 and calibration unit (HSE), Stereoscope (Olympus, Japan), Digital micro manipulator (HSE), Manipulator, Anti- vibration table (TMC, USA), Faraday cage, Fiber optic illuminator (HSE), Current and Voltage clamp amplifier (axon Instruments, USA), stimulators (grass instruments, USA), Micro- pipette puller model pp-83 (Narishige, Japan) Current source ISO 10 and ISO -50 (home made) supplying 10 and 50mA correspondingly and Oscilloscope,

20MHz (Gould, England), Computers: PowerPC 9500/I50, (Apple, USA), or Pentium, 166MHz, Data Acquisition Boards: PCI-MIO-16XE50, 16 bite, or the PCI-M1O-16E-2, 12 bite board by National Instrument, software: LabView for windows, by National Instrument (USA). Data acquisition and analysis program are home made, The program includes data acquisition and on-line analysis, programmable experiment execution, programmable signal output. The off-line analysis program analyze different parameters of muscle twitch and action potentials.

Solution:

The Krebs-Heseleit Solution (KHS) was prepared using materials from Sigma (Israel): 0.32 g/lit KCl (4.5 mM), 6.99 g/lit NaCl (118.0 mM), 2.01 g/lit $NaHCO_3$ (24.0 mM), 0.285 g/lit $MgSO_4 \bullet 7H_2O$ (1.19 mM), 0.16 g/lit KH_2PO_4 (1.18 mM), 2.0 g/lit Glucose (11.0 mM), and 0.37 g/lit $CaCl_2 \bullet 2H_2O$ (2.52 mM), added after bubbling with a 95% O_2 + 5% CO_2 gas mixture for 20 minutes.

Solution preparation: Distilled water (ion exchange column Zilion, Israel and ultra filtration by EasypurLF, Israel) are used to prepare the KHS stock solution (X 20, 5L). The chemicals except $CaCl_2$ are used. The stock solution is discarded after 1 week of refrigeration, For each day of experiment fresh solution is prepared (5L) out of the stock solution, $CaCl_2$ is added, and the solution is bubbled (95% O_2/5% CO_2) for 20 min. and titrated to a pH of 7.4. Bubbled KHS at room temperature is used for

perfusion of the papillary muscle kept in an organ bath.

Anesthesia and heart dissection: animal is brought from the cage to a scale for measuring body weight, The animal is anesthetized by 1Vembutal 1-1.2 mg /Kg body weight I.P, using -5cc syringe and 23 Gage needle. The level of anesthesia is checked by the animal reflex to a pinch. When the animal is deeply anesthetized, the skin over the chest is cut off and the chest wall is cut open exposing the heart. Using scissors and a forceps the pericardium is cut and the heart is dissected out by cutting all the blood vessels, Immediately after cutting, the heart is placed in an ice cold (4°C) and oxygenated KHS.

Papillary muscle dissection: The heart is transferred to a fresh ice-cold KHS and than to the dissection chamber, containing ice-cold continuously oxygenated KHS. The heart is fixed to a rubber pad with insect pins and than the left ventricle is opened exposing the papillary muscles. A silk (6 0) thread is tied around the tendon of the papillary muscle and the muscle is dissected out using fine twizers. The dissected muscle (length of 2-3mm) is transferred to the organ bath and the heart is kept at 4°C for further dissections of the other papillary muscles.

The Steiert Organ Bath: The muscle is placed in an organ bath, and than fixed to the chamber by a plastic holder. The silk thread tied to the tendon is hooked to a rigid hook on the force transducer (on the opposite

side) to give isometric conditions. The papillary muscle is continuously perfused (7- 12ml/min,) with oxygenated KHS kept at a regulated temperature of 37°C.

Pacing and Stimulation:

Pacing stimuli (typically 1Hz, 2ms duration, and amplitude of 2mA) are given by two Ag-AgCl electrodes which are part of the organ bath and are placed under the muscle. The electrodes are covered with AgCl layer, chlorodizing by 5mA, 5ms pulses during perfusion. Constant current stimuli (NT-signal) are given to the upper part of the muscle using graphite electrodes (diameter of 0.5mm fitted to a glass pipette) placed 2-3mm apart along the fibers' line(contraction axis). The muscle length is adjusted to maximal isometric force and left for equilibration period of 30 min.

Protocol for Acute experiments

Cardiac Inhibition

Equipment

The following equipment which will be referred to hereinafter, is now briefly described for the sake of clarity:

Plugsys system: The plugsys system is an incorporating plug in modules for measuring, controlling and data processing in connection with recorders and computers. In general, it functions as an amplifier which increases the sensitivity of the measuring of biological signals. One such device, used in the experiments described herein, is manufactured by HSE, Germany.

Millar: This device (manufactured by Millar Instruments, USA), is a micro manometers transducer that can be connected to a battery operated bridge (which is the interface box) and the output can be digitized using an A/D converter. In another mode of operation the transducer is connected through a DBA (plugsys DC Bridge Amplifier), which is an amplifier connected to transducers to measure pressure force (manufactured by HSE, Germany).

1. Premedication and anesthesia

1.1 Dogs are premedicated (sedated) with morphine sulfate (2 mg/kg) I.M.

1.1.1.Wait 30 min.

1.2 Open 2 IV lines

1.2.1 Anesthesia is performed using α-chloralose: (freshly prepared in the morning of the experiment using: 2 gr. sodium tetraborate, 6 gr. α-chloralose and 30 gr. of urethane dissolved in 300 cc water heated to 60°C

and than cooled to 37°C before IV administration). A good anesthetic level is achieved when the corneal reflex is absent.

1.3. Infuse 500 cc Ringer Lactate during the first 15 min. after accomplishment of anesthesia. Continuous infusion of Ringer Lactate at a rate of 5 cc/min via the second IV line.

1.4. Continuous anesthesia is given with a pump charged with a 50 cc syringe filled with α-chloralose-urethane solution at an infusion rate of 0.15 cc/min.

2. Mechanical Ventilation

Immediately after the animal is anesthetized artificial ventilation is set on, The animal is intubated using an endotracheal tube (#7-8.5) and ventilated with room air at 14-20 rpm, output phase ratio 50%, stroke volume between 300-400 cc (depending on dog size).

3. Hemodynamic measurements

3.1. EKG: Remove hair from areas where EKG patches are positioned, at both anterior legs and left posterior leg.

3.2. Open arterial line: The right and left femoral artery are exposed and introducer sheets (8.5F) are inserted. The introducer sheet are prewashed with saline-heparin (2500 units/dl).

3.3 Millar Transducer calibration: 7F Millar pressure transducers are used for measuring both left ventricular pressure (LVP) and arterial blood pressure (BP).

3.4 Blood pressure: BP is obtained from another Millar transducer introduced into the other femoral artery after calibration,

3.5 Jugular veins: the left jugular vein is exposed and 8.5- 9F introducer sheet is applied to insert a pacing electrode into the right ventricle under X-Ray if needed.

3.6 Left ventricular catheterization: Using X-ray the Millar catheter is inserted into the LV.

4. Surgical procedures

4.1 Monitoring heart rate. Heart rate is carefully monitored before chest opening. Rise in the heart rate upon chest opening is prevented by administration of Fentanyl Citrate (3-4 μg/kg IV) 5-10 min. before incision is made.

4.2 Chest incision. Chest is opened through a middline incision with a diathermic-cauterizing blade set to the lowest possible power. The blade is used to cut the skin and muscle layers above the sternum. Bleeding is promptly stopped to achieve stabilization of animal hemodynamics. The chest is maintained open with a retractor for only short periods as needed. Body temperature is controlled with an infrared

lamp 50-80 cm above the chest area.

5. **Electrical and hemodynamic monitoring**

5.1 Aortic flow. Aortic flow (cardiac output) is measured by placing a Transonic Doppler flow meter transducer on the thoracic descending aorta. Calibrate the ultrasound probe in a plastic cup filled with saline to zero flow while 'Mea' button is pressed. Check that the appropriate key for each probe is connected to the Transonic flow meter (model T106, TRANSONIC, USA). Once the reading is zero it can be placed and secured with a screw driver (probes of 6, 10 and 12 mm). The transducer yields averaged and pulsate blood flows into the acquisition system.

5.2. Arterial blood pressure. The Millar transducer is connected to a Plugsys. The signal is filtered at 300 Hz and fed into the acquisition system.

5.3. Left ventricular pressure. The animal LVP is measured using a catheter tip micro manometers (Millar Instruments, USA) inserted into to the left ventricle either throughout the left or right femoral artery. The micro manometers transducer is connected to a battery operated bridge and the output will be digitized using A/D converter.

5.4 EKG. Surface EKG is measured using the standard EKG leads connected to the animal limbs. The signal is amplified with a BPA unit (bipotential amplifier module for direct measurement of EKG, manufactured by HSE, Germany) on a Plugsys amplifier.

6. Data acquisition

Sampling is carried using National Instruments AT-MIO data acquisition board. The board allows simultaneous acquisition up to 8 differential channels. The sampling rate is up to 200 KHz. The sampling used in the system is 1 KHz per channel. The acquired data can be displayed on line on the computer monitor and saved on the computer disk for further data analysis. The printouts shown in the figures were obtained from the above setup.

7. Detailed description of the experimental setup:

A bipolar pacing electrode was inserted into the heart and placed near the apex of the RV using an X-Ray. Carbon screw electrodes (home made) were placed at the base (epicardially) of the LV and three at the apex as schematically illustrated in Fig. 1.

Acquisition setup:

Channel 0 = NT signal

Channel 1 = LVP

Channel 2 = Mean Aortic flow

Channel 3 = EKG -body surface

Channel 4 = Blood pressure

Channel 5 = Pulsate aortic flow

Channel 6 = Changed according to the protocol

Channel 7 = Pacing

Example 1

In Vitro Effect of Polarity of Muscle Contraction

Papillary muscle tissue was removed from the left ventricle of a rabbit, according to the protocol described above. The tissue was placed in a Steiert Organ Bath Type 813 (HSE, Germany) in which the experiment was carried out.

The muscle was excited at a rate of 1 pulse per second (1 Hz). The polarity of the NT signal was inverse to that which caused an increase in the muscle contractility.

The muscle was caused to contract by the application of a pacing signal at 1 Hz, 4 millisecond duration of 2 mA amplitude. 5 Milliseconds after the pacing signal, a non-excitatory signal of 5 milliampers was applied during 150 milliseconds. The result is shown in Fig. 2, which shows the timing

and magnitude of the electric signal (NT-signal - Fig. 2A), and the force of contraction of the muscle, measured as explained above (Fig. 2B).

The same experiments as in Fig. 2 are shown in Fig. 3, with higher time resolution, showing only the effect of NT-signal application on two muscle contractions (twitches). The dashed line represents the contraction force when the NT signal is applied.

Example 2

Example 1 was repeated while on the same muscle tissue, with a pacing of 1 Hz, a pacing signal of 4 mA for a period of 2 milliseconds. The non-excitatory signal (NT-signal) of 5 mA was applied with a 5 mS delay, and for 100 milliseconds thereafter. Three different situations were tested: "+NT-signal", with a positive polarity "-NT-signal", with a negative polarity, and "Control", without the application of a NT-signal. The signs of the polarity are taken so that "+NT-signal" indicates an increase in contractility, and "-NT-signal" indicates a decrease in contractility. The results are shown in Fig. 4, where Fig. 4A shows the behavior of the force in the different situations, and Fig. 4B shows a summary of data from three experiments where decrease in muscle contractility was achieved by changing the polarity of the signal, going from left to right: there is a decrease of over 20% in peak force compared to the control, there is a 35% increase in the contraction width as measured at 10% of base-peak, there

is a decrease in dp/dt (in the papillary muscle dp/dt means the rate of change in the development of contraction force), which represents the developing of force in the ascending limb of the twitch (an increase in dp/dt is considered an increase in contractility), but there is a very significant decrease in -dp/dt, which is the relaxation from the twitch (descending limb of the twitch) indicating reduction in the efficacy of the muscle contraction.

Example 3

A dog was prepared for an *in-vivo* experiment, as described in detail in the above Protocol. The dog's heart was paced using a pace maker, at 160 heartbeats per minute. Carbon electrodes were positioned at the base of the left ventricle (cathode) and at the edge of the ventricle (anode), and a current was caused to flow between them 60 milliseconds after the pacing signal was delivered to the right ventricle. The current was 8 mA, and was continued for 50 milliseconds. The current pulse caused a reduction in heart output, as well as in the contractility of the cardiac muscle cells, as calculated from the developed pressure of the left ventricle.

The results are seen in Fig. 5, where Fig. 5A shows the decrease in LVP pressure, and Fig. 5B shows the decrease in cardiac output (mean aortic flow). From both results the reduction of the contractility of the beating heart *in vivo* is clearly demonstrated.

Example 4

Operating as in Example 3, The heart was simultaneously paced (150 b.p.m.) with a physiologic electrode within the apex of the right ventricle, and Medtronics epicardial electrodes at the right auricle.

LVP was measured with a Millar transducer catheter located within the left ventricle. Cardiac output was evaluated with a 12 mm ultrasonic probe (Transonic) positioned after the aortic arch in the thoracic aorta.

NT signals were delivered epicardially with electrodes located at the posterior side of the left ventricle. The apical electrode (+) was located at mid-way between the apex and the base (-). The basal electrode was positioned between Circumflex and the Right Coronary artery. The electrical current delivered was 8 mA, delay from the pacing pulse was 40 msec, and duration of the pulse was 30 msec.

Results: The results are shown in Fig. 6, in which Fig. 6A is the decrease in pressure, and Fig. 6B is the decrease in output (blood flow rate). The mean aortic flow decreased 6% relative to the baseline during the application of the NT signal. The Left ventricular pressure showed decreases in:

peak amplitude ratio: -7.6%

peak width ratio: -0.3%

+dP/dt -15%

-dP/dt -25%

Example 5

Operating as in Example 3, the heart was simultaneously paced (140 b.p.m.) with a physiologic electrode within the apex of the right ventricle, and Medtronics epicardial electrodes at the right auricle.

LVP was measured with a Millar transducer catheter located within the left ventricle, Cardiac output was evaluated with a 12 mm ultrasonic probe (Transonic) positioned after the aortic arch in the thoracic aorta.

NT signals were delivered epicardially with electrodes located at the posterior side of the left ventricle. The apical electrode (+) was located at mid-way between the apex and the base (-). The basal electrode was positioned between Circumflex and the Right Coronary arteries. The electrical current delivered was 8 mA, delay from the pacing pulse was 40 msec, and duration of the pulse was 30 msec.

Results: The results are shown in Fig. 7. Fig. 7A shows the decrease in pressure, and Fig. 7B shows the decrease in blood flow rate. The mean aortic flow decreased by 11.9% relative to the baseline during the

application of the NT signal. The left ventricular pressure showed decreases in:

peak amplitude ratio: -8.6% (compared to baseline)

peak width ratio: -2.6% (compared to control)

+dP/dt: -3.9%

-dP/dt: -30.3%

Example 6

Long Duration Sub-Critical Signal

Sub-critical non-excitatory signal (NT-signal) is a current that will not induce a new contraction in the cardiac muscle, because its amplitude is sub-critical, viz., its magnitude is not enough to cause pacing, and which therefore also meets the requirements for non excitatory signal as described above.

Long duration Sub-critical NT-signal (Sub-NT-signal) can reduce the peak force of contraction during pacing. An organ bath experiments on rabbit left ventricle papillary muscle was carried out.

Parameters:

Pacing: 1 Hz, 2ms duration, 4mA.

Sub-NT-signal: 5mS delay, 995 mS, 0.5mA.

The results are shown in Fig. 8, which shows a decrease of about 20% in the peak force induced by Sub-NT-signal during pacing. Sub-NT-signal

alone does not cause contraction. This is shown in the trace when the pacing stimulation is turned off.

Example 7

Example 1 was repeated, under the following conditions: The muscle was paced at 1Hz, 2 mA amplitude, 2 msec duration. NT signals were applied at 30 msec delay, 60 msec duration, and amplitude of 6 mA. The polarities were switched (+ and - signs), to show the effect of the polarity on the contractility. The results are shown in Fig. 9, from which the decrease in force of the muscle is clearly seen, when a "-" polarity is applied, and an increase when a "+" polarity is applied. Once again, the "+" and "-" signs are arbitrary, and indicate the result as detailed above.

Example 8

Operating as in Example 1, a long duration NT-signal was applied to the left ventricular papillary muscle from rabbit. The parameters employed were:

Pacing: 0.5 Hz, 2mS duration, 3.5 mA.

NT-signal: 1 mS delay, 1999 mS duration, 10 mA.

The results are shown in Fig. 10, from which it can be seen that an about 75% decrease in peak force is induced by the NT-signal during pacing.

Stopping pacing (upper trace), but not the NT signal (middle trace) stopped the muscle contraction (lower trace).

It should be noted that the non-excitatory nature of the NT signal employed in this experiment derives from its length, and not from its magnitude. Accordingly, this experiment illustrates another type of NT signal useful for reducing contractility.

Referring now to Fig. 11, a schematic representation of an apparatus according to one embodiment of the invention is seen. In this scheme, a portion of a cardiac muscle, H, is brought into closed positioned relationship with two electrodes, E1 and E2, the ends of which are positioned at root position R1 and R2, respectively. The electrodes receive the voltage and current from a signal generator S, the construction of which is conventional and well know to skilled persons, and which is therefore not described here in detail, which in turn receives power from a power line, PL, connected to an autonomous power source or to the mains, as the case may be. The activity of the power signal generator S is controlled by a controller, C, which may be a microprocessor, or which may be an external controlling device, e.g., a PC or other computer. The controller C controls the parameters of the signal generated by the signal generator, such as current intensity, frequency and timing, and may use both preset parameters (e.g., the frequency of pulse generation) and feed-back input, e.g., from apparatus which monitors heart or other

parameters, or from a pace maker which supplies the pacing signal. These input signals are collectively schematically indicated in the figure as FB. Of course, the apparatus is only schematically shown, for the sake of brevity. And the skilled person will easily be able to devise many different kinds of apparatus suitable to supply the signal needed in carrying out the invention.

All the above description and examples have been given for the purpose of illustration, and are not intended to limit the invention in any way. Many modifications can be effected in the apparatus and method of the invention. For instance, different electrodes can be used, with different currents, for different periods of times; various areas of the heart can be provided with electrodes and treated therewith, and different devices can be provided, whether implanted or external, for temporary or continued treatment, all without exceeding the scope of the invention.

Claims

1. Apparatus comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of a muscle.

2. Apparatus as claimed in claim 1, comprising circuitry for controlling the start time of the electric potential generated between said at least two points.

3. Apparatus as claimed in claim 1, comprising circuitry for controlling the duration of the electric potential generated between said at least two points.

4. Apparatus as claimed in claim 1, comprising circuitry for controlling the magnitude of the electric potential generated between said at least two points.

5. Apparatus as claimed in claim 1, for use in reducing the contraction force of a muscle.

6. Apparatus as claimed in claim 5, wherein the muscle is a cardiac muscle.

7. Apparatus as claimed in claim 1, wherein the circuitry for creating a non-excitatory electric potential between said at least two points comprises one or more electrode.

8. Apparatus as claimed in claim 7, wherein the electrodes are carbon electrodes.

9. Apparatus as claimed in claim 1, which is an insertable device.

10. Apparatus as claimed in claim 1, which is an extra corporal device.

11. Apparatus as claimed in claim 1, which is an implantable device.

12. Apparatus as claimed in claim 2 or 3, wherein the circuitry for controlling the start time and/or duration of the electric potential is synchronized to heart activity.

13. Apparatus as claimed in claim 12, wherein the circuitry for controlling the start time and/or duration of the electric potential operate not at every beat of the heart.

14. Apparatus as claimed in claim 13, wherein the circuitry for controlling the start time and/or duration of the electric potential operates every 1, 2 or 3 beats of the heart.

15. Apparatus comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of a muscle.

16. Apparatus as claimed in claim 15, comprising circuitry for controlling the start time of the electric current flowing between said at least two points.

17. Apparatus as claimed in claim 15, comprising circuitry for controlling the duration of the electric current flowing between said at least two points.

18. Apparatus as claimed in claim 15, comprising circuitry for controlling the magnitude of the electric current flowing between said at least two points.

19. Apparatus as claimed in claim 15, for use in reducing the contraction force of a muscle.

20. Apparatus as claimed in claim 19, wherein the muscle is a cardiac muscle.

21. Apparatus as claimed in claim 15, wherein the circuitry for causing a non-excitatory electric current to flow between said at least two points comprises one or more electrode.

22. Apparatus as claimed in claim 21, wherein the electrodes are carbon electrodes.

23. Apparatus as claimed in claim 15, which is an insertable device.

24. Apparatus as claimed in claim 15, which is an extra corporal device.

25. Apparatus as claimed in claim 15, which is an implantable device.

26. Apparatus as claimed in claim 16 or 17, wherein the circuitry for controlling the start time and/or duration of the electric current is synchronized to heart activity.

27. Apparatus as claimed in claim 25, wherein the circuitry for controlling the start time and/or duration of the electric current operate not at every beat of the heart.

28. Apparatus as claimed in claim 27, wherein the circuitry for controlling the start time and/or duration of the electric current operates every 1, 2 or 3 beats of the heart.

29. Apparatus as claimed in any one of claims 1 to 28, wherein the non-excitatory electric signal is a DC electric signal.

30. Apparatus as claimed in any one of claims 1 to 28, wherein the non-excitatory electric current is a DC electric current.

31. Apparatus for reducing the contraction force of a muscle, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle.

32. Apparatus for reducing the contraction force of a muscle, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle.

33. Apparatus for selectively and reversibly reducing the oxygen consumption of an area of a muscle, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle.

34. Apparatus for selectively and reversibly reducing the oxygen consumption of an area of a muscle, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle.

35. Apparatus for performing heart surgery, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of the cardiac muscle.

36. Apparatus for performing heart surgery, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of the cardiac muscle.

37. Apparatus as claimed in claim 35 or 36, wherein the heart surgery is a bypass operation.

38. Apparatus as claimed in claim 35 or 36, wherein the heart surgery is a minimal invasive cardiac operation.

39. Apparatus for promoting the healing of the hibernated area of the cardiac muscle after myocardial infarct, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of said hibernated area.

40. Apparatus for promoting the healing of the hibernated area of the cardiac muscle after myocardial infarct, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of said hibernated area.

41. Apparatus for promoting the healing of an ischemic area of the cardiac muscle, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of said ischemic area.

42. Apparatus for promoting the healing an ischemic area of the cardiac muscle, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of said ischemic area.

43. Apparatus for treating congenital or acquired hypertrophic cardiomyopathy, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of said hypertrophic area.

44. Apparatus for treating congenital or acquired hypertrophic cardiomyopathy, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of said hypertrophic area.

45. Apparatus for aiding in performing cardiac ablation, comprising circuitry for creating a non-excitatory electric potential between at least two points located in the vicinity of the area to be ablated.

46. Apparatus for aiding in performing cardiac ablation, comprising circuitry for causing a non-excitatory electric current to flow between at least two points located in the vicinity of the area to be ablated.

47. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, comprising circuitry for controlling the start time of the electric potential generated between said at least two points.

48. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, comprising circuitry for controlling the duration of the electric potential generated between said at least two points.

49. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, comprising circuitry for controlling the magnitude of the electric potential generated between said at least two points.

50. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, wherein the circuitry for creating a non-excitatory electric potential between said at least two points comprises one or more electrode.

51. Apparatus as claimed in claim 50, wherein the electrodes are carbon electrodes.

52. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, which is an insertable device.

53. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, which is an extra corporal device.

54. Apparatus as claimed in any one of claims 32, 35, 38, 39, 41, 43 or 45, which is an implantable device.

55. Apparatus as claimed in claim 47, wherein the circuitry for controlling the start time of the electric potential is synchronized to heart activity.

56. Apparatus as claimed in claim 48, wherein the circuitry for controlling the duration of the electric potential is synchronized to heart activity.

57. Apparatus as claimed in claim 55 or 56, wherein the circuitry for controlling the start time and/or duration of the electric potential operate not at every beat of the heart.

58. Apparatus as claimed in claim 57, wherein the circuitry for controlling the start time and/or duration of the electric potential operates every 1, 2 or 3 beats of the heart.

59. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, comprising circuitry for controlling the start time of the electric current flowing between said at least two points.

60. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, comprising circuitry for controlling the duration of the electric current flowing between said at least two points.

61. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, comprising circuitry for controlling the magnitude of the electric current flowing between said at least two points.

62. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, for use in reducing the contraction force of a muscle.

63. Apparatus as claimed in claim 62, wherein the muscle is a cardiac muscle.

64. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, wherein the circuitry for causing a non-excitatory electric current to flow between said at least two points comprises one or more electrode.

65. Apparatus as claimed in claim 64, wherein the electrodes are carbon electrodes.

66. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, which is an insertable device.

67. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, which is an extra corporal device.

68. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, which is an implantable device.

69. Apparatus as claimed in claim 60, wherein the circuitry for controlling the start time and/or duration of the electric current is synchronized to heart activity.

70. Apparatus as claimed in claim 69, wherein the circuitry for controlling the start time and/or duration of the electric current operate not at every beat of the heart.

71. Apparatus as claimed in claim 70, wherein the circuitry for controlling the start time and/or duration of the electric current operates every 1, 2 or 3 beats of the heart.

72. Apparatus as claimed in any one of claims 33, 36, 38, 40, 42, 44 or 46, wherein the non-excitatory electric current is a DC electric current.

73. Apparatus as claimed in claim 72, further comprising signal generation circuitry for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

74. Apparatus for reducing the contraction force of a muscle, comprising:

- means for creating an electric potential between at least two points located in the vicinity of the muscle;

- means for causing a non-excitatory DC electric current to flow between said at least two point, if desired; and

- means for controlling the start time, duration and magnitude of the non-excitatory electric potential and/or of the non-excitatory electric current flowing between said at least two points.

75. Apparatus according to claim 74, comprising:

- means for creating an electric potential between at least a pair of electrodes in the vicinity of the muscle at at least two root locations;

- means for causing a non-excitatory DC electric current to flow between said at least two root locations when desired; and

- means for controlling the start time, duration and magnitude of the non-excitatory electric potential and/or of the non-excitatory electric current flowing between said at least two root locations.

76. Apparatus according to claim 74 or 75, further comprising means for superimposing on the DC signal one or more waveforms of given frequency and amplitude, thereby to generate a complex signal.

77. A method for reducing the contraction force of a muscle, comprising creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points.

78. A method for reducing the contraction force of a muscle, comprising causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points.

79. A method according to claim 77 or 78, wherein the muscle is a cardiac muscle.

80. A method according to claim 78, wherein the non-excitatory electric current is a DC current.

81. A method according to claim 80, further comprising generating a complex signal by superimposing on the DC signal one or more waveforms of given frequency and amplitude.

82. A method according to any one of claims 78 to 81, wherein the flow of the non-excitatory DC electric current is synchronized to heart activity.

83. A method according to claim 82, wherein the non-excitatory DC electric current flows not at every beat of the heart.

84. A method according to claim 83, wherein the non-excitatory DC electric current to flows every 1, 2 or 3 beats of the heart.

85. A method for performing heart surgery, comprising reducing the contraction force of a treated area of the cardiac muscle, by creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points,

thereby to obtain the desired reduction in muscle contraction at the treated heart area and thereafter performing surgery thereon.

86. A method for performing heart surgery, comprising reducing the contraction force of a treated area of the cardiac muscle, by causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, thereby to obtain the desired reduction in muscle contraction at the treated heart area and thereafter performing surgery thereon.

87. A method according to claim 85 or 86, wherein the heart surgery is a bypass operation.

88. A method according to claim 85 or 86, wherein the heart surgery is a minimal invasive cardiac operation.

89. A method for promoting the healing of the cardiac muscle after myocardial infarct, comprising creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points, said electric potential being of an

intensity and polarity suitable to obtain the desired reduction in muscle contraction at the affected heart area.

90. A method for promoting the healing of the cardiac muscle after myocardial infarct, comprising causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, said electric current being of an intensity and polarity suitable to obtain the desired reduction in muscle contraction at the affected heart area.

91. A method for selectively and reversibly reducing the oxygen consumption of an area of a muscle, comprising causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, said electric current being of an intensity and polarity suitable to obtain the desired reduction in oxygen consumption at the affected heart area.

92. A method for selectively and reversibly reducing the oxygen consumption of an area of a muscle, comprising creating a non-excitatory electric potential between at least two points located in the vicinity of the

muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of said non-excitatory electric potential, said electric potential being of an intensity and polarity suitable to obtain the desired reduction in oxygen consumption at the affected heart area.

93. A method for treating congenital or acquired hypertrophic cardiomyopathy, comprising reducing the contraction force of a the heart muscle by creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points, said electric potential being of an intensity and polarity suitable to obtain the desired reduction in muscle contraction.

94. A method for treating congenital or acquired hypertrophic cardiomyopathy, comprising reducing the contraction force of a the heart muscle by causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, said electric current being of an intensity and polarity suitable to obtain the desired reduction in muscle contraction.

95. A method for performing cardiac ablation, comprising reducing the contraction force of the area of the cardiac muscle to be ablated, by creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric potential created between said at least two points, thereby to obtain the desired reduction in muscle contraction at the heart area to be ablated, and thereafter performing the ablation thereon.

96. A method for performing cardiac ablation, comprising reducing the contraction force of the area of the cardiac muscle to be ablated, by causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, and controlling one or more of the parameters consisting of start time, duration, magnitude and polarity of the non-excitatory electric current flowing between said at least two points, thereby to obtain the desired reduction in muscle contraction at the heart area to be ablated, and thereafter performing the ablation thereon.

97. A method according to any one of claims 86, 90, 91, 94 or 96, wherein the non-excitatory electric current is a DC current.

98. A method according to claim 97, further comprising generating a complex signal by superimposing on the DC signal one or more waveforms of given frequency and amplitude.

99. A method according to any one of claims 86, 90, 91, 94 or 96, wherein the flow of the non-excitatory DC electric current is synchronized to heart activity.

100. A method according to claim 99, wherein the non-excitatory DC electric current flows not at every beat of the heart.

101. A method according to claim 100, wherein the non-excitatory DC electric current to flows every 1, 2 or 3 beats of the heart.

102. A method according to any one of claims 86 to 94, wherein the cardiac muscle contractility is increased at locations other than the treated location.

103. A method for the interim treatment of a heart in need of reducing oxygen consumption, comprising reducing the contraction force of a the heart muscle by creating a non-excitatory electric potential between at least two points located in the vicinity of the muscle, of an intensity and polarity suitable to obtain the desired reduction in muscle contraction at

the treated heart area, thereby reducing the oxygen consumption of the heart.

104. A method for the interim treatment of a heart in need of reducing oxygen consumption, comprising reducing the contraction force of a the heart muscle by causing a non-excitatory electric current to flow between at least two points located in the vicinity of the muscle, of an intensity and polarity suitable to obtain the desired reduction in muscle contraction at the treated heart area, thereby reducing the oxygen consumption of the heart.

105. A method according to claim 104, wherein the non-excitatory electric current is a DC current.

106. A method according to claim 105, further comprising generating a complex signal by superimposing on the DC signal one or more waveforms of given frequency and amplitude.

107. A method according to claim 104, wherein the flow of the non-excitatory DC electric current is synchronized to heart activity.

108. A method according to claim 108, wherein the non-excitatory DC electric current flows not at every beat of the heart.

109. A method according to claim 108, wherein the non-excitatory DC electric current to flows every 1, 2 or 3 beats of the heart.

110. A method for reducing the contraction force of a muscle, comprising:

- providing means for creating an electric potential between at least two points located in the vicinity of the muscle;

- providing means for causing a non-excitatory DC electric current to flow between said at least two point;

- providing means for switching the current polarity between said at least two points; and

- providing means for controlling the start time, duration and magnitude of the electric current flowing between said at least two points.

111. A method according to claim 110, comprising:

- providing an electric potential between at least a pair of electrodes in the vicinity of the muscle at at least two root locations;

- causing a non-excitatory DC electric current to flow between said at least two contacting locations;

- providing means for switching the current polarity between said root locations; and

- controlling the start time, duration and magnitude of the electric current flowing between said at least two root locations, so as to obtain the desired reduction in muscle contraction.

112. A method according to claim 110 or 111, further comprising generating a complex signal by superimposing on the DC signal one or more waveforms of given frequency and amplitude.

113. A method according to any one of claims 110 to 112, wherein the means for causing a non-excitatory DC electric current to flow, are synchronized to heart activity.

114. A method according to claim 113, wherein the means for causing a non-excitatory DC electric current to flow operate not at every beat of the heart.

115. A method according to claim 114, wherein the means for causing a non-excitatory DC electric current to flow operate every 1, 2 or 3 beats of the heart.

116. Apparatus for reducing the contraction force of a muscle, essentially as described and illustrated.

117. A method for reducing the contraction force of a muscle, essentially as described, and with particular reference to the examples.

118. A method for performing heart surgery, essentially as described, and with particular reference to the examples.

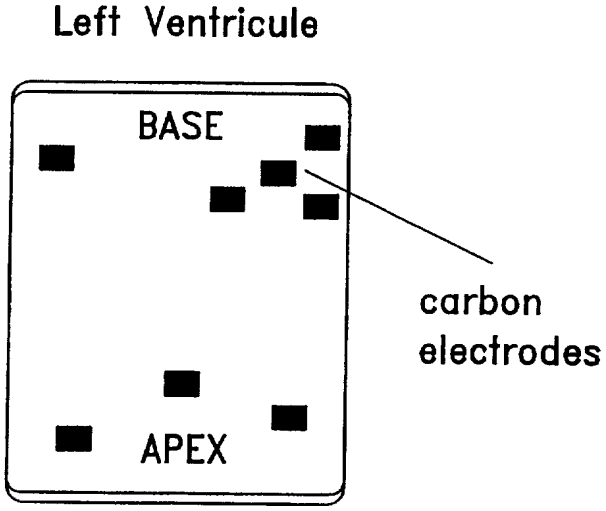


Fig. 1

Fig. 2A

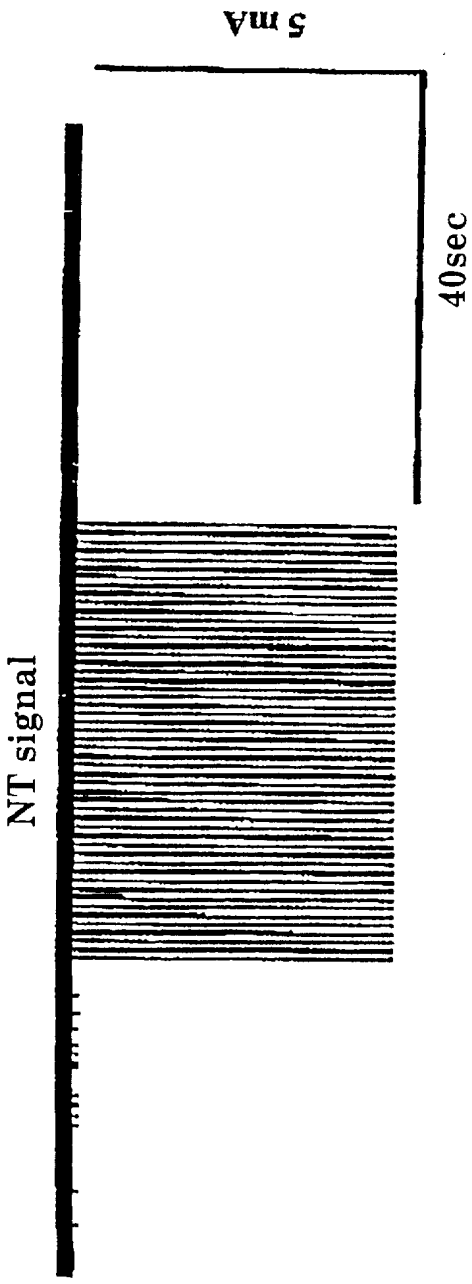


Fig. 2B

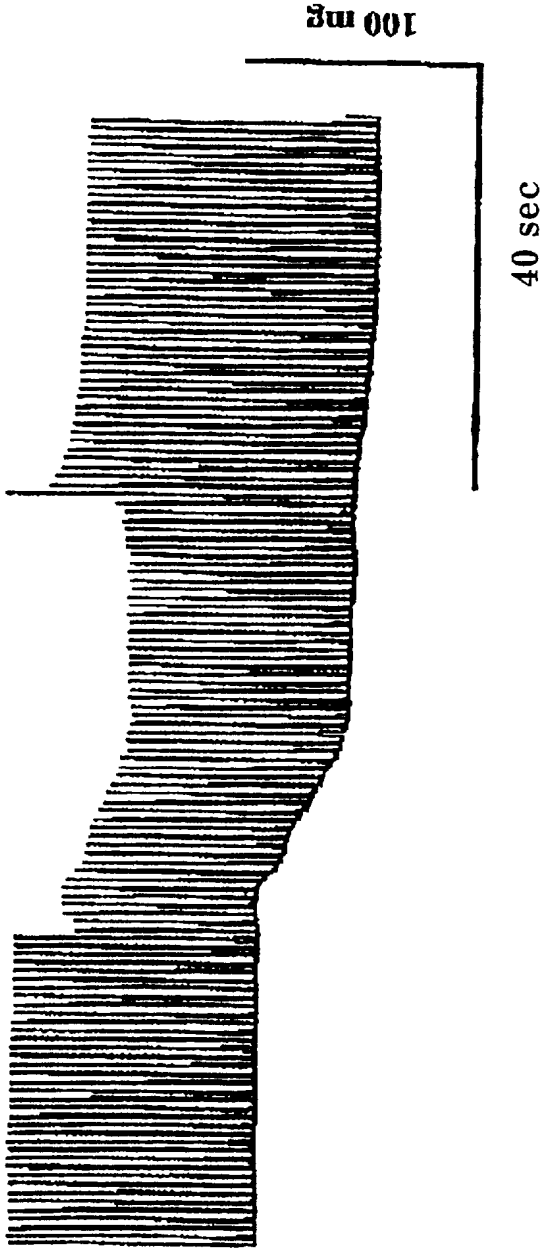


Fig. 3A

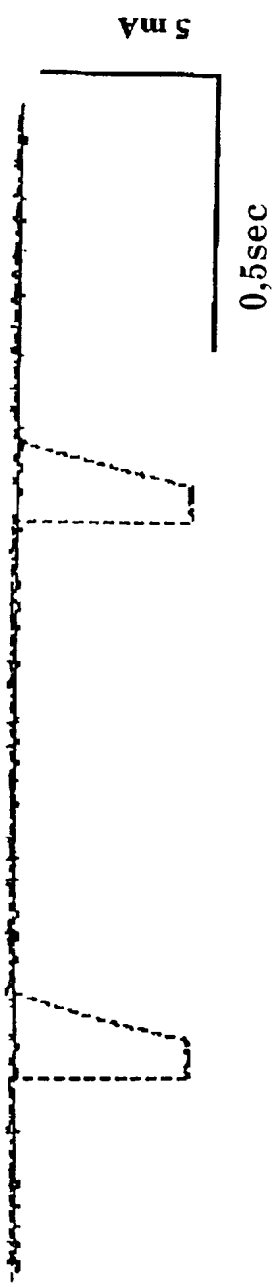
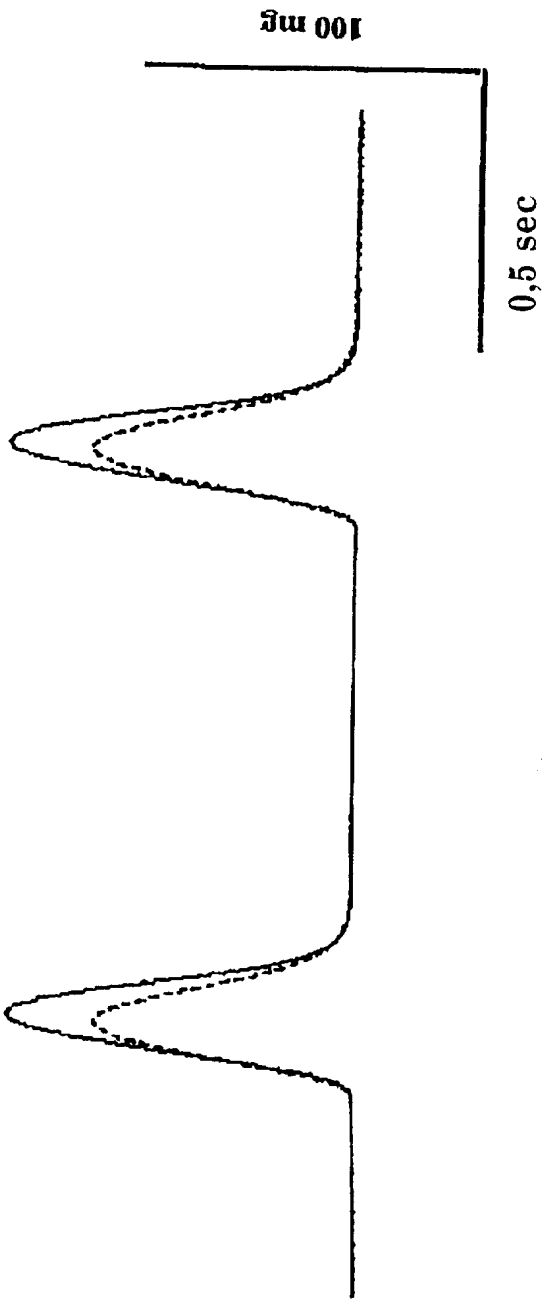


Fig. 3B



4/11

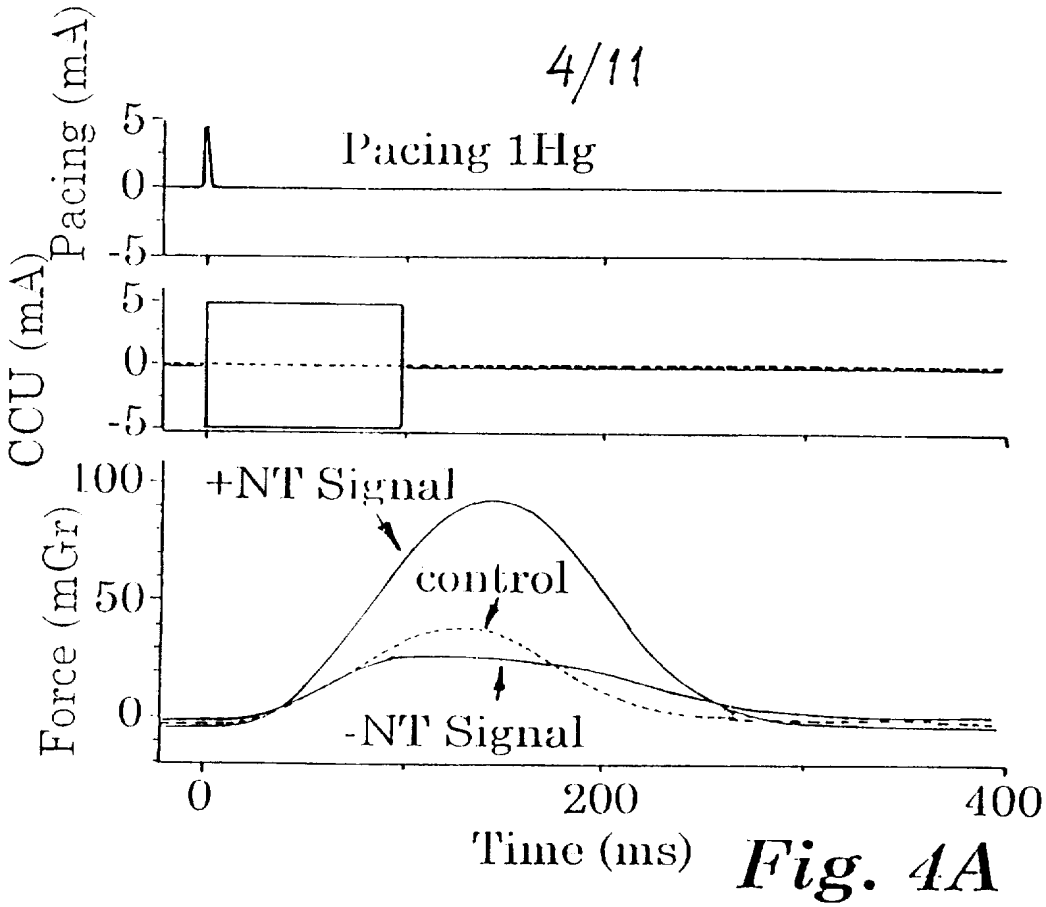


Fig. 4A

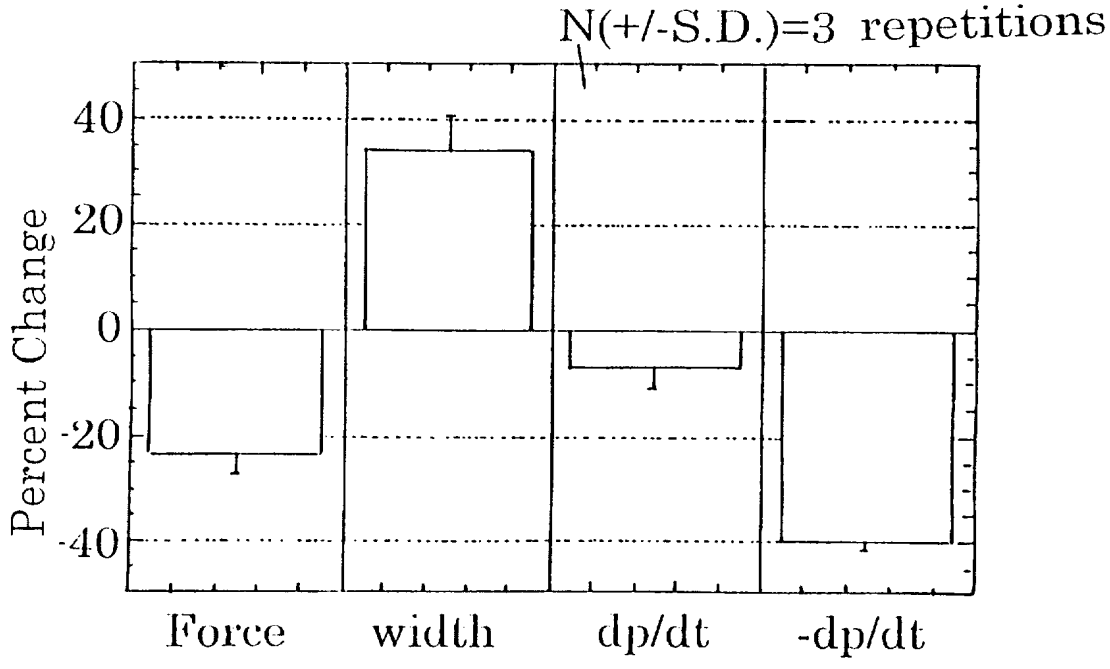


Fig. 4B

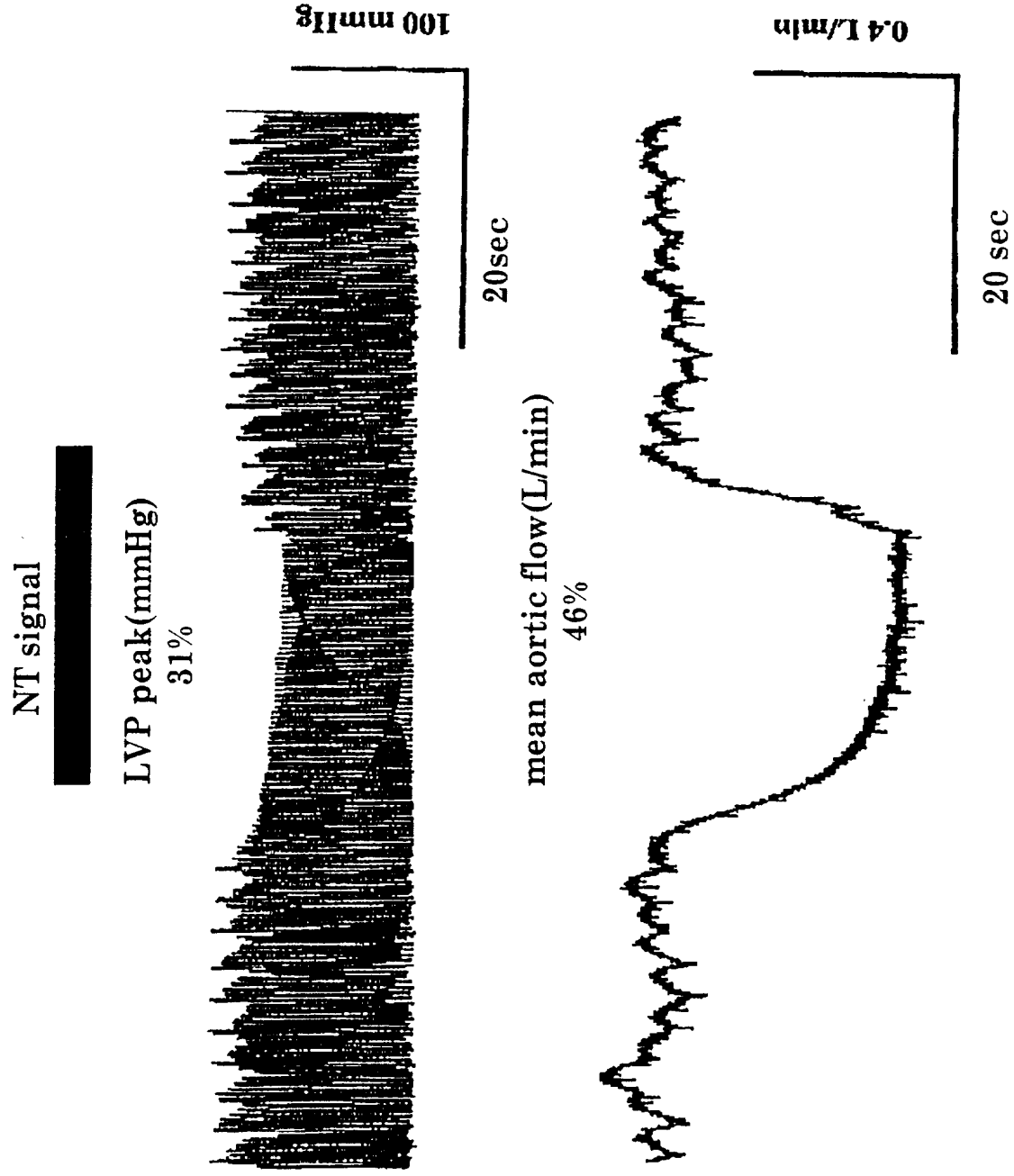

NT signal
LVP peak(mmHg)
31%
100 mmHg
20sec
mean aortic flow(L/min)
46%
0.4 L/min
20 sec

Fig. 5A

Fig. 5B

Fig. 6A

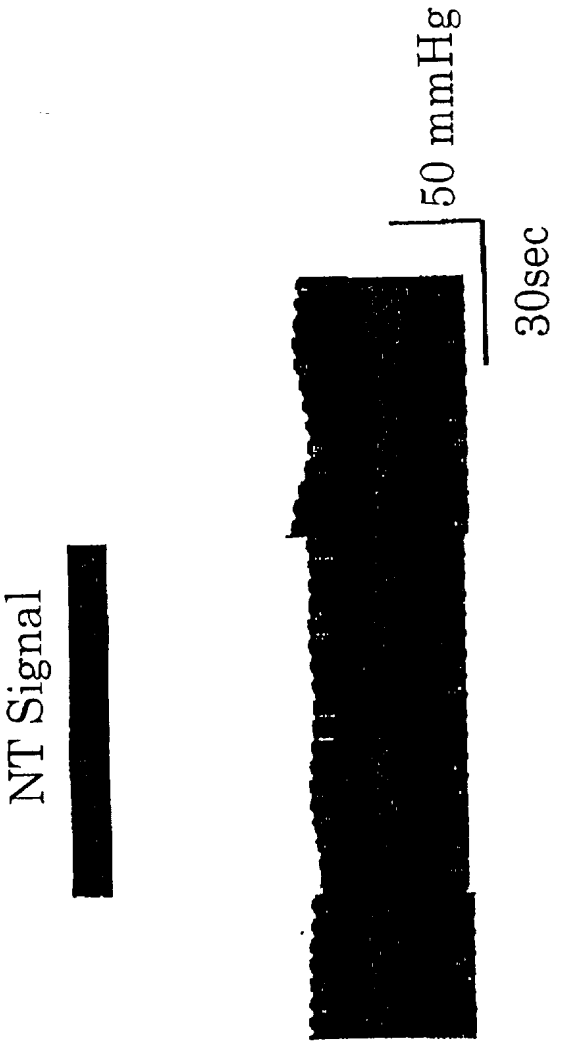


Fig. 6B

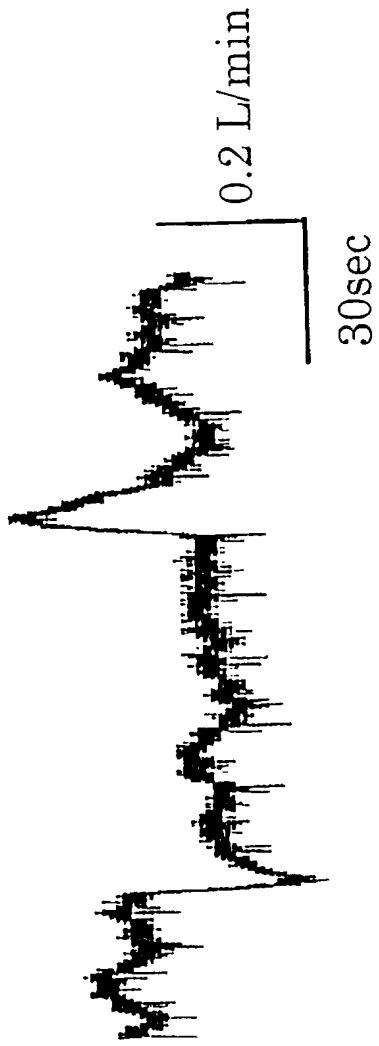


Fig. 7A

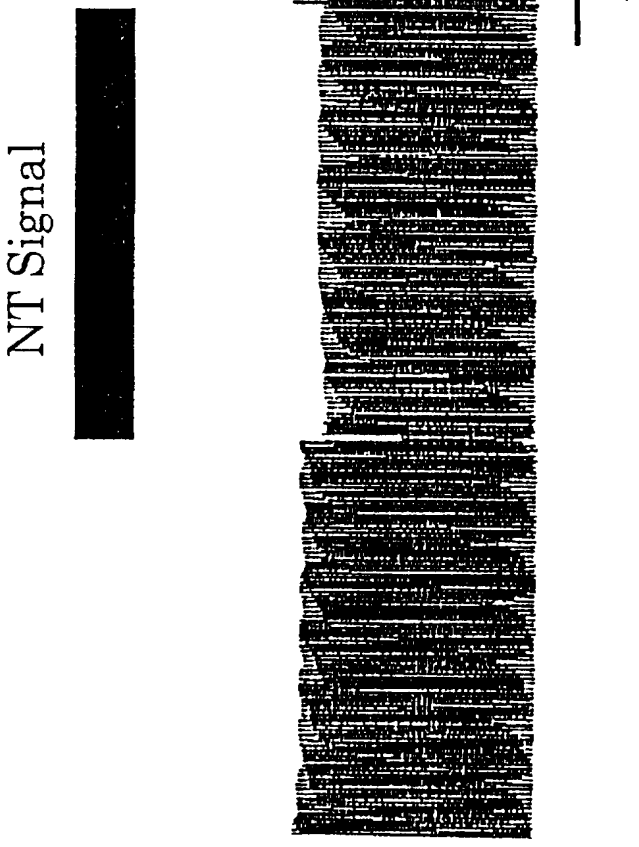
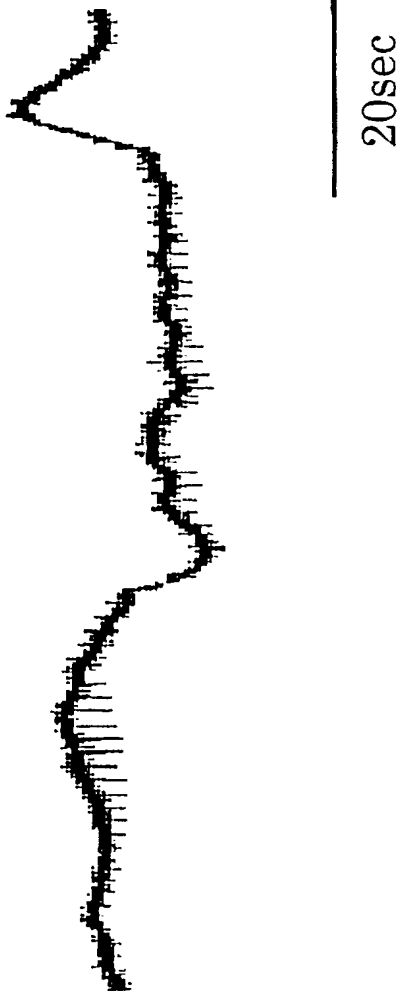


Fig. 7B



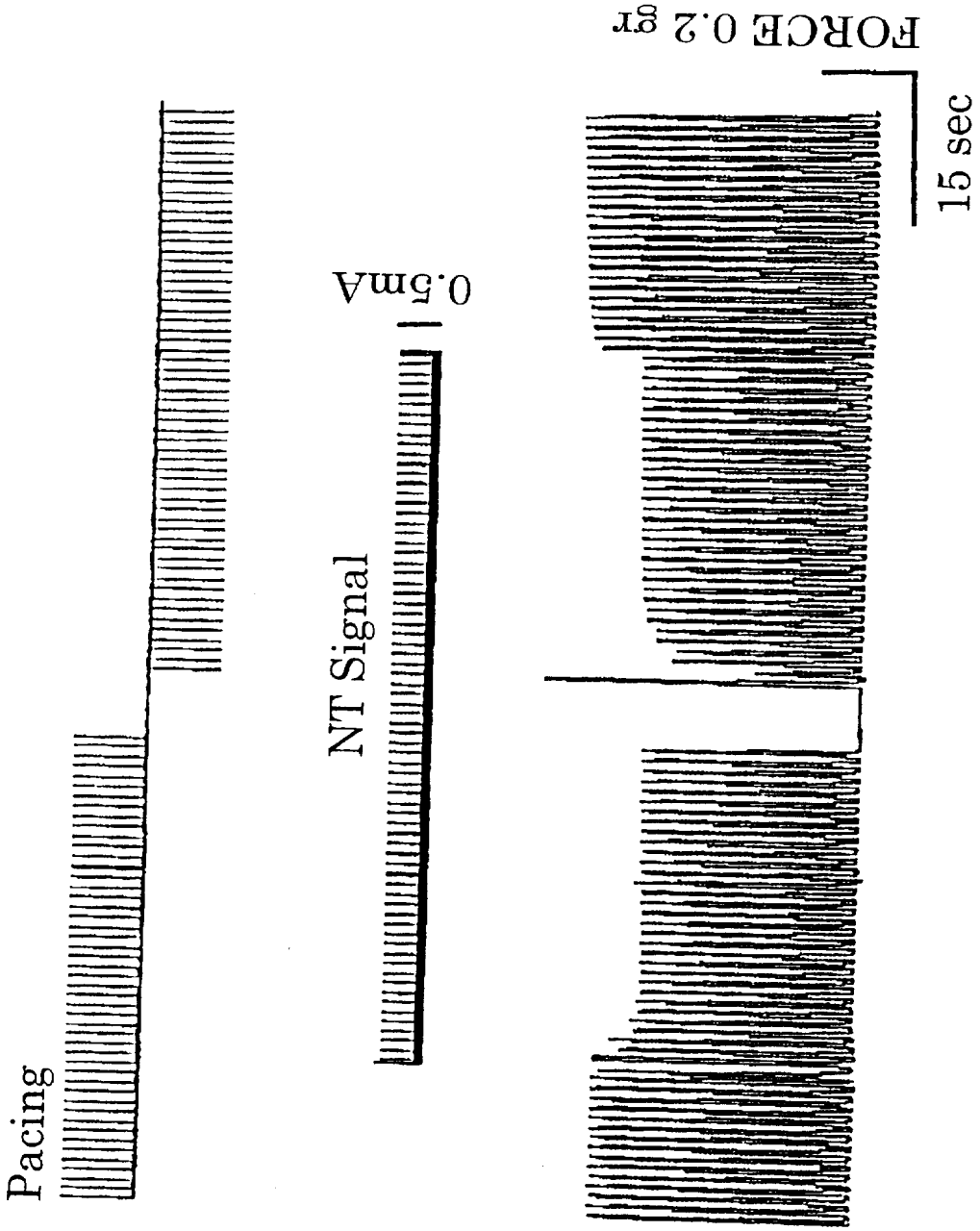


Fig. 8

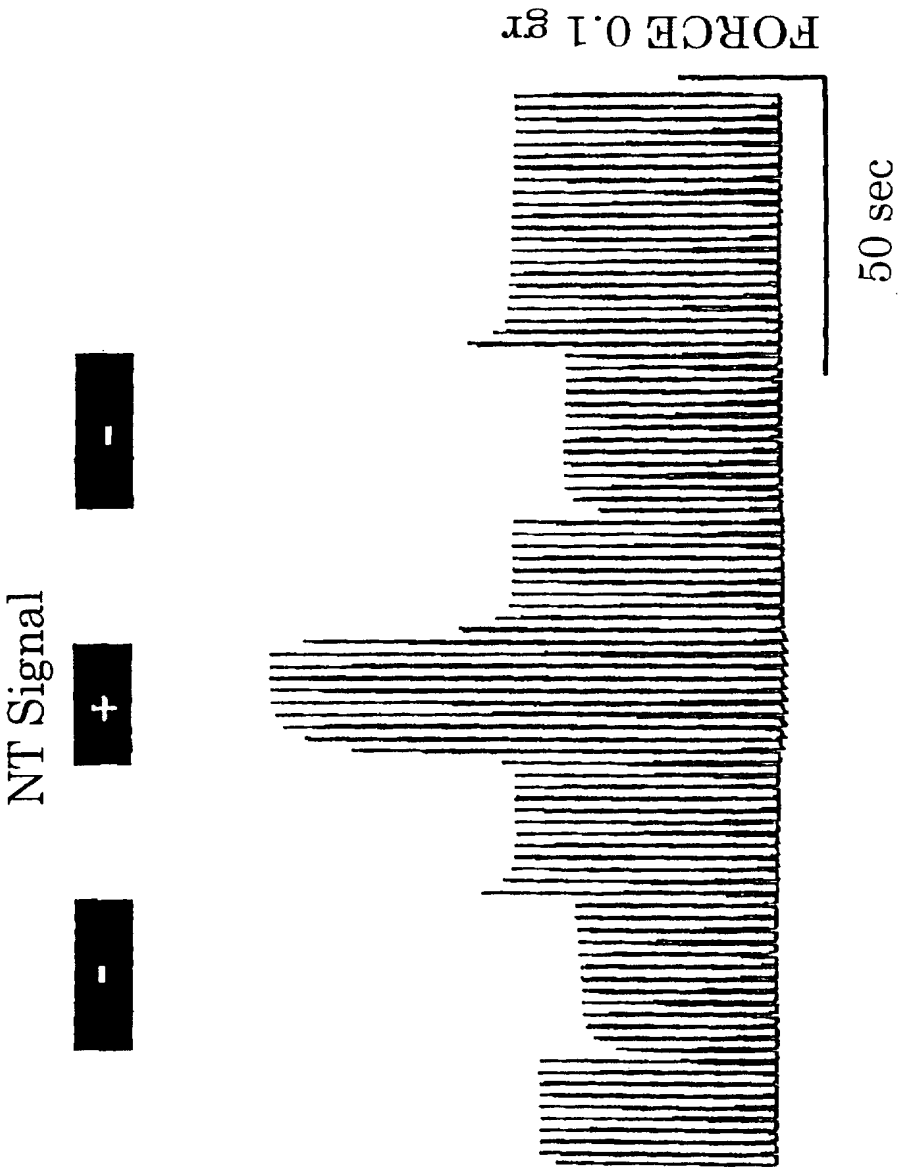


Fig. 9

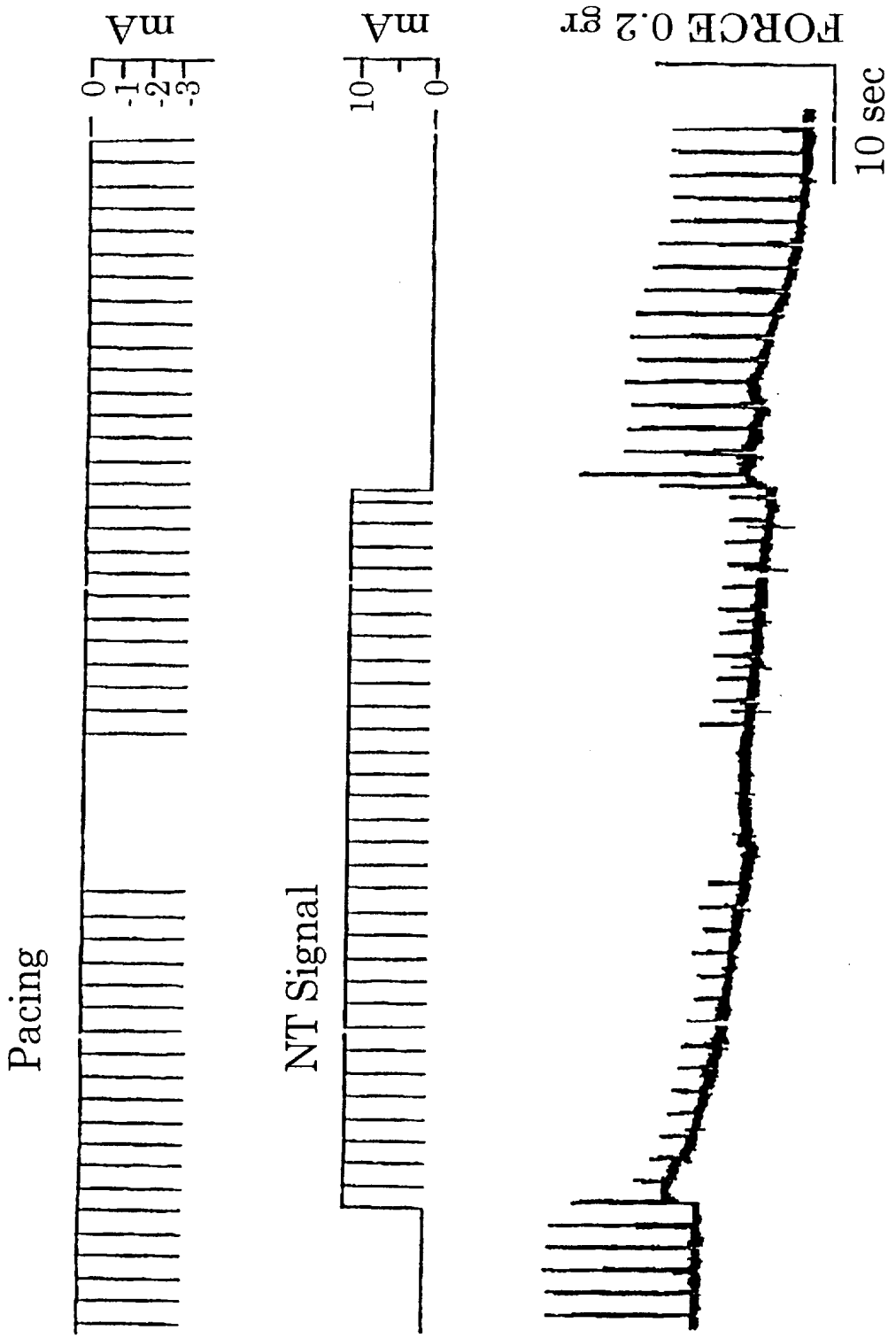


Fig. 10

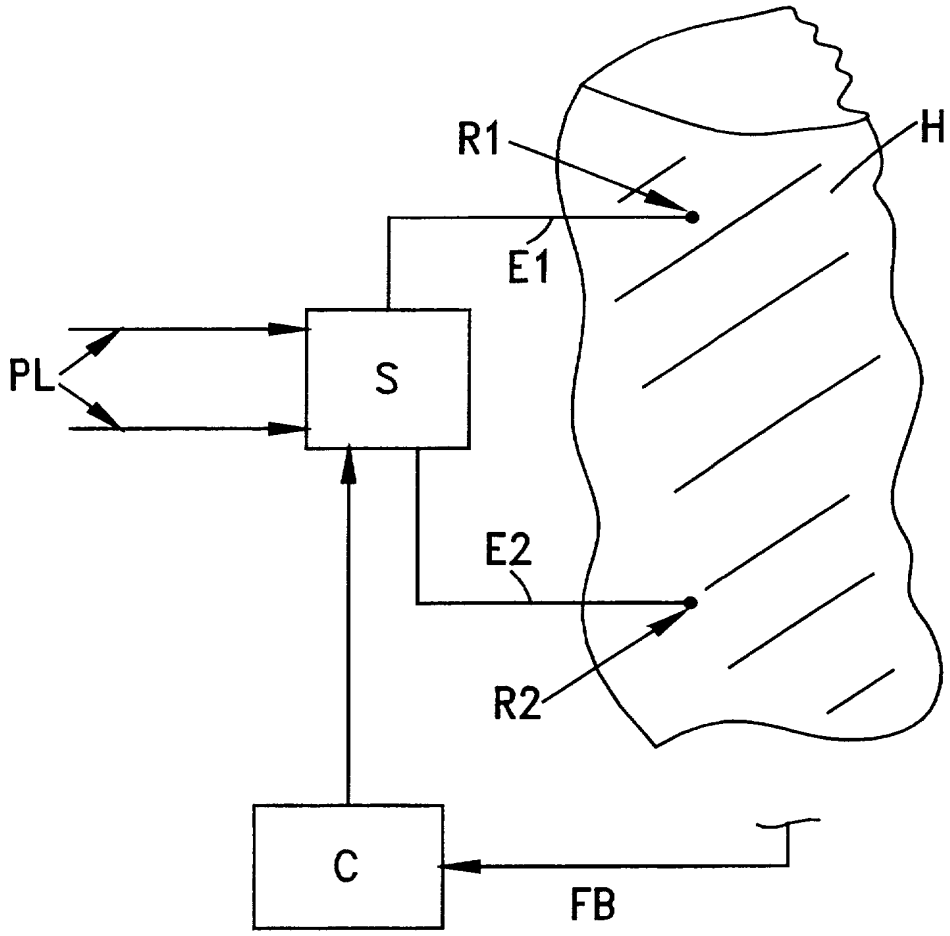


Fig. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL97/00231

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61N 1/362
US CL : 607/009

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/009, 010

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,083,564 A (SCHERLAG) 28 January 1992, entire document.	1-76

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 SEPTEMBER 1997	Date of mailing of the international search report 03 OCT 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Diane L. Smith for JEFFREY R. JASTRZAB Telephone No. (703) 308-2097

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL97/00231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 77-118
because they relate to subject matter not required to be searched by this Authority, namely:

A search is not required for medical methods per PCT Rule 39.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.